would be forced to perform undue experimentation in order to fulfill the invention as claimed.

Applicant, however, respectfully notes that, for reasons given in more detail below, the present Application provides teachings of antibodies which are capable of specifically binding to heparanases which are less than 80% homologous to SEQ ID NO:2; that predictability of protein function is not required because an assay for heparanase activity is taught in the present Application, which could easily be performed by one of ordinary skill in the art; and that the teachings of the present Application provide a clear recitation of structure and function with regard to the claimed antibodies.

Specifically, Applicant notes that the Examiner has stated that the present Application does not describe an antibody against a polypeptide having heparanase activity which shares at least 90% homology with SEQ ID NO:2 (or the equivalent in the parent application, SEQ ID NO:10). Applicant respectfully disagrees, as the present Application describes specific examples (species) of anti-heparanase antibodies against particular peptides, within the larger genus of anti-heparanase antibodies. This larger genus includes antibodies which are capable of recognizing heparanases having even widely disparate amino acid sequences. For example, p. 12, lines 13-16 of the present Application state that the antibodies described therein are capable of recognizing the mouse B16-F10 heparanase as well as human platelet heparanases and heparanase enzymes produced by several human tumor cell lines and CHO cells (see also Figures 18-20 for experimental evidence). However, the mouse heparanase amino acid sequence is known to have less than 80% homology to human heparanase, as described in published PCT Application No. WO 00/52178: POLYNUCLEOTIDE ENCODING A POLYPEPTIDE HAVING HEPARANASE ACTIVITY AND EXPRESSION OF SAME IN GENETICALLY MODIFIED CELLS. Furthermore, sequence information available about a variant of the B16-F10 cell line shows that the sequence of heparanase in the cell line is apparently identical to the sequence of heparanase in regular mouse tissue. Therefore, actual experimental support (in the form of examples) is provided for antibodies that specifically recognize heparanase sequences that have even less than about 90% homology, which can even recognize those sequences having less than about 80% homology.

To further clarify this point, Applicant has submitted alignment data in the attached Appendix, showing the homology (and differences) between human, rat, mouse and chicken heparanase sequences. Some important shared features such as the heparanase binding site are marked. This information further supports Applicant's statements with regard to both the antibodies of the present invention, and also the ability of one of ordinary skill in the art to readily recognize a heparanase protein as such.

The parent application, US Ser. No. 08/922,170 (now US Patent No. 5,968,822), clearly states that anti-heparanase antibodies, whether polyclonal or monoclonal, may be raised against the recombinant heparanase enzyme (p. 18, lines 23-end; also on p. 23, lines 25-end). The same parent application states that the recombinant heparanase taught therein also includes heparanases having 90% or 80% homology to the specific described sequences. This portion has now been incorporated into the present Application by amendment, as described in greater detail below. Therefore, the parent application provides a basic description of anti-heparanase antibodies being capable of recognizing heparanases having 90% or 80% homology to the specific described sequences; both degrees of homology are now being claimed in the present Application.

Applicant notes that according to the revised "Guidelines for the Examination of Patent Applications Under the 35 USC 112, paragraph 1, 'Written Description' Requirement", section IB ("New or Amended Claims"), the guidelines clearly state that "there is no *in haec verba* requirement", such that the wording of the new or amended claims does not need to be literally present in the specification. Instead, it is sufficient if the wording is "supported in the specification through express, implicit, or inherent disclosure".

Thus, from the parent application and the present Application, it is clear that the genuses of anti-heparanase antibodies capable of recognizing heparanases having 90% or 80% homology to the specific described sequences are taught. Furthermore, examples are taught of antibodies capable of recognizing heparanases having even less than 80% homology to the taught human heparanase sequences.

A further rejection raised by the Examiner is that one of ordinary skill in the art would not know which changes in the heparanase sequence could be made while preserving heparanase function. Applicant notes that the present Application clearly

teaches an assay for heparanase activity, as described on p. 40, line 21 to the end, bridging to p. 41, lines 1-13. Such an assay could easily be used by one of ordinary skill in the art to determine which proteins having a sequence that falls within the definition of homology (90% or 80%) in the claim also have heparanase activity.

The Examiner has stated that the problem of predicting which changes can be tolerated falls well outside the realm of routine experimentation. However, Applicant notes that the teaching of the assay for heparanase activity removes this difficulty, because such an assay could easily be routinely performed by one of ordinary skill in the art. Applicant further notes that the definition of "one of ordinary skill in the art" has been held in numerous court cases to depend upon the art in question; in fields such as that of the present invention, clearly the art would indicate that "one of ordinary skill in the art" could actually be a team of Ph.D. level scientists. Such a team could easily perform the taught assay in the present Application without undue experimentation.

The Examiner has also described a paper by Zhou et al., which teaches that mutations in the HFE protein have profound effects on its activity. Applicant respectfully traverses this further rejection by noting that the heparanase family of proteins is not related to the HFE protein. On the contrary, the members of the heparanase family of proteins share a similar function with at least somewhat dissimilar sequences, in terms of the percentage homology. As previously described, Applicant has submitted alignment data in the attached Appendix, showing the homology (and differences) between human, rat, mouse and chicken heparanase sequences.

The Examiner also stated that the above claims were rejected due to a lack of working examples. However, multiple examples of both polyclonal and monoclonal antibodies are provided which are capable of recognizing human, mouse and hamster heparanase; see Figures 18-20. As noted above, mouse heparanase (from the mouse melanoma cell line) has less than 80% homology to human heparanase, for example. Thus, multiple working examples are provided of antibodies that are capable of recognizing both human heparanase and also heparanase having a sequence that is at least less than about 90% homologous, and preferably up to about 80% homologous.

The provision of multiple species clearly supports the enablement of the overall genus of anti-heparanase antibodies. Applicant notes that the revised Guidelines state in

footnote 42 that "examples of identifying characteristics include sequence, structure, binding affinity, binding specificity, molecular weight and length.... For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities or antibody cross-reactivity". The teachings of the present Application are therefore clearly sufficient to support a nexus between structure and function: the structure of the antibody is defined in terms of the protein that it must recognize, which in turn has a clearly structural limitation of being at least 90% homologous (or optionally at least 80% homologous) to the specific taught heparanase sequences. The protein itself is further described in terms of its function, which may be determined through a specific taught assay. Such a limitation is also a functional limitation on the antibody itself.

In order to further clarify these aspects of the present invention, Applicant has chosen to amend the present Application to incorporate teachings from the parent application, US Patent Application No. 08/922,170, now US Patent No. 5,968,822 as follows. Support is given in terms of page and line numbers from the parent application (rather than the patent as issued).

With regard to the added paragraph on p. 20, which shows support for the teachings of different percentages of homology of the amino acid sequence to SEQ ID NO:10 (identical to the instant SEQ ID NO:2, also as stated by the Examiner) it should be noted that support can be found on p. 11, lines 14-18. Support for the teachings of how to determine homology can be found on p. 28, lines 15-19.

Applicant therefore feels that these arguments overcome the Examiner's rejections in this regard.

Rejections over 35 USC 112, second paragraph

The Examiner has rejected claims 1-10 over 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner has stated that the parent application does not describe how to obtain 90% homology, and that clarification is required with regard to the algorithm used to determine 90% homology, as recited in the parent application. The rejections of the Examiner are respectfully traversed.

In the parent application, p. 28, lines 15-19 (all page and line numbers are taken from the application itself rather than from the issued patent), a description is provided of sequence analysis and alignment being performed with the sequence analysis software package developed by the Genetic Computer Group (GCG) at the University of Wisconsin. This description is sufficient to determine how the percentage homologies were obtained, because this package performs an alignment between sequences. The exact nature of the alignment with regard to whether gaps are introduced, for example, may differ according to the setting of the parameters. However, when overall homologies are being discussed, as in this instance, the percentage of such homology does not change radically according to different parameters that are chosen. This is because percentage homology is a global measure of similarity between two sequences, which is not significantly affected by local aspects of sequence alignment. However, the choice of different parameters has a great effect on local features of the sequence alignment, but has a much reduced effect (if any) on the global percentage homology. Thus, the description provided in the parent application is certainly sufficient to teach one of skill in this particular art (protein sequence alignment) how to determine the global measure of homology between two sequences.

This description of how to determine homology between two sequences has been incorporated from the parent application into the present Application as previously described.

Applicant therefore feels that these arguments overcome the Examiner's rejections in this regard.

Double Patenting Rejection

The Examiner has rejected claims 1-10 under the judicially created doctrine of non-obviousness type double patenting as being anticipated by U.S. Patent No. 6,177,545.

A terminal disclaimer in compliance with 37 CFR 1.321(c) and which overcomes the Examiner's rejections is enclosed herewith.

For the reasons given above, Applicant feels that claims 1-12 are in condition for allowance. A prompt Notice of Allowance is respectfully requested.

Respectfully submitted,

Sol Sheinbein
Registration No. 25,457

Date: 26 May 2003

APPENDIX - Sequence Homology Data

```
                    10        20        30        40        50        60
                     |         |         |         |         |         |
mouse       -MLR-------LLLLWLWGPLGALAQGAPAGTAPTDDVVDLEFYTKRPLRSVSPSFLSIT
rat         -MLRP------LLLLWLWGRLRALTQGTPAGTAPTKDVVDLEFYTKRLFQSVSPSFLSIT
human       MLLRSKPALPPPLMLLLLGPLGPLSPGALPRPAQAQDVVDLDFFTQEPLHLVSPSFLSVT
chicken     ----------MLVLLLLVLLLAVPP--------RR-TAELQLGLREPIGAVSPAFLSLT
                      *:* *   * .:.             ..:*::  :. :  ***:***:*

                    70        80        90       100       110       120
                     |         |         |         |         |         |
mouse       IDASLATDPRFLTFLGSPRLRALARGLSPAYLRFGGTKTDFLIFDPDKEPTSEERSYWKS
rat         IDASLATDPRFLTFLGSPRLRALARGLSPAYLRFGGTKTDFLIFDPNKEPTSEERSYWQS
human       IDANLATDPRFLILLGSPKLRTLARGLSPAYLRFGGTKTDFLIFDPKKESTFEERSYWQS
chicken     LDASLARDPRFVALLRHPKLHTLASGLSPGFLRFGGTSTDFLIFNPNKDSTWEEKVLSEF
            :**.** ****: :*  *:*::** ****.:****** ******:*.*:.* **:  :

                   130       140       150       160       170       180
                     |         |         |         |         |         |
mouse       QVNHDICRSEPVSAAVLRKLQVEVPFQELLLLREQYQKEFKNSTYSRSSVDMLYSFAKCS
rat         QDNNDICGSERVSADVLRKLQMEVPFQELLLLREQYQREFKNSTYSRSSVDMLYSFAKCS
human       QVNQDICKYGSIPPDVEKKLRLEVPYQEQLLLREHYQKKFKNSTYSRSSVDVLYTFANCS
chicken     QAK-DVCEAWPSFAVVPKLLLTQVPLQEKLLLAEHSWKKHKNTTITRSTLDILHTFASSS
            * : *:*       . * . *   :** ** *** *:  ::.**:* :**::*:*::**..*

                   190       200       210       220       230       240
                     |         |         |         |         |         |
mous        GLDLIFGLNALLRTPDLRWNSSNAQLLLDYCSSKGYNISWELGNEPNSFWKKAHILIDGL
rat         RLDLIFGLNALLRTPDLRWNSSNAQLLLNYCSSKGYNISWELGNEPNSFWKKAQISIDGL
human       GLDLIFGLNALLRTADLQWNSSNAQLLLDYCSSKGYNISWELGNEPNSFLKKADIFINGS
chicken     GFRLVFGLNALLRRAGLQWDSSNAKQLLGYCAQRSYNISWELGNEPNSFRKRSGICIDGF
             : *:********* ..*:*:****: **.**:.:.************** **: * *:*

                   250       260       270       280       290       300
                     |         |         |         |         |         |
mouse       QLGEDFVELHKLLQRS-AFQNAKLYGPDIGQPRGKTVKLLRSFLKAGGEVIDSLTWHHYY
rat         QLGEDFVELHKLLQKS-AFQNAKLYGPDIGQPRGKTVKLLRSFLKAGGEVIDSLTWHHYY
human       QLGEDYIQLHKLLRKS-TFKNAKLYGPDVGQPRRKTAKMLKSFLKAGGEVIDSVTWHHYY
chicken     QLGRDFVHLRQLLSQHPLYSHAELYGLDVGQPRRHTQHLLRSFMKSGGKAIDSVTWHHYY
            ***.*::.*::** :   :::*:*** *:**** :* ::*:**:*:**:.***:******

                   310       320       330       340       350       360
                     |         |         |         |         |         |
mouse       LNGRIATKEDFLSSDALDTFILSVQKILKVTKEITPGKKVWLGETSSAYGGGAPLLSNTF
rat         LNGRVATKEDFLSSDVLDTFILSVQKILKVTKEMTPGKKVWLGETSSAYGGGAPLLSNTF
human       LNGRTATREDFLNPDVLDIFISSVQKVFQVVESTRPGKKVWLGETSSAYGGGAPLLSDTF
chicken     VNGRSATREDFLSPEVLDSFATAIHDVLGIVEATVPGKKVWLGETGSAYGGGAPQLSNTY
            :*** **:****..:.** *  :::.:: :.:   **********.******** **:*:

                   370       380       390       400       410       420
                     |         |         |         |         |         |
mouse       AAGFMWLDKLGLSAQMGIEVVMRQVFFGAGNYHLVDENFEPLPDYWLSLLFKKLVGPRVL
rat         AAGFMWLDKLGLSAQLGIEVVMRQVFFGAGNYHLVDENFEPLPDYWLSLLFKKLVGPKVL
human       AAGFMWLDKLGLSARMGIEVVMRQVFFGAGNYHLVDENFDPLPDYWLSLLFKKLVGTKVL
chicken     VAGFMWLDKLGLAARRGIDVVMRQVSFGAGSYHLVDAGFKPLPDYWLSLLYKRLVGTRVL
            .***********:*: **:****** ****.***** .*.**********:*:***.:**

                   430       440       450       460       470       480
                     |         |         |         |         |         |
mouse       LSRVKGPDRSKLRVYLHCTNVYHPRYQEGDLTLYVLNLHNVTKHLKVPPPLFRKPVDTYL
rat         MSRVKGPDRSKLRVYLHCTNVYHPRYREGDLTLYVLNLHNVTKHLKLPPPMFSRPVDKYL
human       MASVQGSKRRKLRVYLHCTNTDNPRYKEGDLTLYAINLHNVTKYLRLPYPFSNKQVDKYL
chicken     QASVEQADARRPRVYLHCTNPRHPKYREGDVTLFALNLSNVTQSLQLPKQLWSKSVDQYL
             : *: ..  : ********  :*:*:***:**:.:** ***: *::*  :  : ** **

                   490       500       510       520       530       540
                     |         |         |         |         |         |
mouse       LKPSGPDGLLSKSVQLNGQILKMVDEQTLPALTEKPLPAGSALSLPAFSYGFFVIRNAKI
rat         LKPFGSDGLLSKSVQLNGQTLKMVDEQTLPALTEKPLPAGSSLSVPAFSYGFFVIRNAKI
```

```
human       LRPLGPHGLLSKSVQLNGLTLKMVDDQTLPPLMEKPLRPGSSLGLPAFSYSFFVIRNAKV
chicken     LLPHGKDSILSREVQLNGRLLQMVDDETLPALHEMALAPGSTLGLPAFSYGFYVIRNAKA
            * * * ..:**:.***** *:***::***.* * .* .**:*.:***** *:*******

mouse       AACI
rat         AACI
human       AACI
chicken     IACI
             ***
```

Multiple alignment of heparanase from Human, Rat, Mouse and chicken generated by Clustal W. Active site residues are bolded and putative heparin binding sites are boxed.